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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/649,400	08/26/2003	William E. Bunney JR.	020885-000720US	6108

20350 7590 01/10/2006

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EXAMINER	
STANDLEY, STEVEN H	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 01/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/649,400	BUNNEY ET AL.	
	Examiner	Art Unit	
	Steven H. Standley	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *2,5,10 and 12-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 4, 6-9, and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-12, in the reply filed on 10/3/05 is acknowledged. The traversal is on the ground(s) that because the inventions are conceptually related, there would not be a substantially greater burden on the examiner. This is not found persuasive because as set forth in the requirement for restriction of 8/30/05, the inventions are distinct and would require non-overlapping searches. For instance, as argued in the requirement for restriction, Group I is directed to a method of diagnosing a patient and Groups II-IV are inventions related to identifying a compound or treating with a compound, polypeptide, or nucleic acid. Thus the inventions have different goals and different steps and would represent a substantial search burden on the examiner. The examiner has further required an election of species. Applicant's election of "SEQ ID NO: 3," "nucleic acid," and "Bipolar disease," with traverse is acknowledged. The examiner has required further species election for the reasons set forth in the requirement for restriction of 8/30/05. Each species represented are patentably distinct, their searches would not be coextensive and therefor would represent a burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL. Claims 2, 5, 10, and 12-50 are withdrawn as directed to non-elected subject matter. Claims 1, 3-4, 6, 7-9, and 11 are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4, 6, 7-9, and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is complex. The invention as recited is a method of determining whether a subject *has* or is *predisposed* for a mental disorder by testing for the presence of a nucleic acid that hybridizes to the sequence of SEQ ID NO: 3 in a generic 'biological sample.' It is complex because the specification teaches a significant change in mRNA measured by *in situ* hybridization in a small region of the *postmortem*

brains of previously diagnosed (and treated) bipolar patients compared to matched controls, but the invention as recited in the claims is to measuring this change in mRNA in a generic 'biological sample,' which could be any fluid or tissue from an individual, in a *living* patient who may be *predisposed* to a (generic) mental disorder (and having never manifested symptoms of a mental disorder). For the invention to work as claimed, this small change in mRNA levels in a small sub region of prefrontal cortex of the transcription factor TBR1 must be measurable in any bodily fluid or tissue which constitutes a biological sample, and this small change must be *predictive or diagnostic* of a mental disorder.

The state of the prior art is silent on any assay wherein a brain specific mRNA of any kind is obtained from a "biological sample" such as amniotic fluid (as recited in claim 7), cerebral spinal fluid, blood, other tissues, or even brain biopsy for the diagnosis of a patient that has or is predisposed to a neurological disorder. The prior art only teaches measuring levels of mRNA levels encoding brain-specific proteins for use in postmortem diagnostics, such as forensics. For instance Iino et al. (2003) teach PCR quantification of FE65 or APP mRNA in postmortem brain for the retrospective diagnosis of brain trauma. Iino et al state that "these results suggest that real-time PCR of FE65 mRNA is useful for the diagnosis of [Diffuse Axonal Injury] DIA in ***forensic cases*** [end of abstract; emphasis added]." However, there are no teachings of measuring brain-specific mRNA in a "biological sample" to diagnose a mental disorder or to predict a mental disorder.

Further, the art teaches measuring ***polypeptides*** (not mRNA) which are brain specific in the serum or cerebral spinal fluid as a measure of traumatic brain injury indicating breakdown of the blood brain barrier (BBB; see Pleines et al, 2001, page 492, 2nd paragraph from top). These brain-specific proteins are ***not present*** in the periphery under normal circumstances and therefor indicate damage has occurred when present (see Table 2, page 494, for instance). The instant invention measures mRNA (which has not been measured in the art) originating from the dorsolateral prefrontal cortex in the *absence of damage to the BBB* wherein molecules originating from the brain are somehow measured even in the presence of strict diffusional barriers such as the BBB. Thus, Pleines et al teaches that the instant invention only works when a patient having a mental disorder *also has a traumatic brain injury*, thereby allowing the measure of brain-specific molecules because the BBB has been compromised. On the other hand, while the markers of Pleines et al are known to be brain specific, the art is also silent as to whether TBR1 is expressed only in the brain or whether it is widely expressed in the periphery. Thus, the art indicates the invention will not work under most circumstances, and that it is unpredictable whether the invention would work if indeed a patient also suffered from, or was made to suffer from for the purposes of diagnosis, traumatic brain injury as well.

The specification provides no working examples relating to how TBR1 would be measured in a generic "biological sample." It only provides In situ mRNA hybridization data from dead patients previously diagnosed bipolar illness. The specification finds about a 30% change in the levels of TBR1 mRNA in layers 3-6 of the dorsalateral

prefrontal cortex of bipolar patients compared to control patients. Furthermore, there is no guidance in the specification as to how to measure this change other than in postmortem patients already having been diagnosed with bipolar illness.

Therefore, given the nature of the invention, the unsupportive nature of the prior art, the lack of any guidance or specific examples in the specification, one skilled in the art would not be able to use the invention as claimed without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-4, 6, 7-9, and 11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step wherein the conditions for determining if the method has worked are recited. For instance, wherein a significant increase in tbr1 in the subject compared to control indicates the subject is predisposed, etc. Claims 3-4, 6, and 7-9, and 11 are rejected as they depend from claim 1.

Claims 1, 3-4, 6, 7-9, and 11 are rejected because stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. The absence of a recitation of clear hybridization conditions (for example, "hybridizes at ***wash*** conditions of 'A'xSSC and 'B'%SDS at 'C' temperature). Claim 1 fails to define the metes and bounds of the varying structures of polynucleotides recited in the claims.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bulfone et al. and Hevner et al (2001) disclose that TBR1 is involved in neuronal differentiation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven Standley whose telephone number is **(571) 272-3432**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on **(571) 272-0867**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Steve Standley, Ph.D.
~~8/7/05~~
8/06/06

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER